NETWORK MECHANISMS FOR LOSS OF CONSCIOUSNESS IN EPILEPSY

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NETWORK MECHANISMS FOR LOSS OF CONSCIOUSNESS IN EPILEPSY.

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We sought to investigate the different patterns of cerebral blood flow (CBF) in complex versus simple partial seizures in order to elucidate possible network mechanisms underlying consciousness. Single photon emission computed tomography (SPECT) ictal-interictal difference imaging was used to compare complex partial seizures (CPS), with impaired consciousness, to simple complex seizures (SPS), with spared consciousness in patients with surgically confirmed mesial temporal epilepsy and lack of recurrent seizures with at least one year follow-up. CPS were studied in the late ictal, defined as 60-90s after seizure onset (N=10), and early postictal, defined as >90s after seizure onset (N=8), periods. SPS were also studied (N=6). A paired t-test model was used for group analysis in SPM99 and correlation analysis was done to study network involvement between brain regions. In the 60-90s CPS group, significant CBF increases were found in the temporal lobe and basal ganglia ipsilateral to seizure onset. In the >90s CPS group, the temporal lobe was no longer activated, but significant hyperperfusion was present in midline subcortical structures and limbic connections. In all CPS patients, there was marked hypoperfusion in the bilateral fronto-parietal association cortex. SPS patients had CBF increases confined only to the temporal lobe and no significant network involvement of midline subcortical structures or the association cortex was seen. Using correlation analysis in all patients (N=24), there was a significant correlation between hyperperfusion in the ipsilateral medial thalamus and hypoperfusion in the ipsilateral frontal association cortex ($r=0.67$, $p<0.001$). In conclusion, loss of consciousness seen in mesial temporal CPS may be due to spread of seizure activity to subcortical midline structures causing long-range network effects including abnormal inhibition of the higher order association areas and abnormal excitation of medial diencephalon and upper brainstem regions.

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INTRODUCTION:

Epilepsy is a very common disorder that causes grave disability in many individuals worldwide. It is a chronic condition characterized by recurrent seizures. Most patients with epilepsy actually have more than one type of seizure. In the US, approximately 2 million people have epilepsy and 3 percent of people will have epilepsy at some point during their lifetimes [1]. With antiepileptic medications, approximately 50-70% of patients with nongenetic localization-related epilepsy can be controlled. However, that leaves at least 30% of patients uncontrolled with medication alone.

Epilepsy syndromes are classified as either generalized, in which the predominant seizure type starts in the cerebral hemispheres bilaterally, or partial, in which the seizure begins in a more localized focus. These two types are separated out both clinically and electrically, via EEG. The initial activation in generalized seizures involves widespread activation of neurons in both hemispheres correlating with an EEG at onset that shows generalized discharges consisting of repetitive spikes, rhythmic slowing, or spike-wave complexes. The onset of seizure activity in a partial seizure involves only a limited number of neurons in one hemisphere and is usually associated with a regional EEG discharge. The EEG is typically rhythmic sharp or slow waves with an evolution over time. Focal epileptic discharges can be seen both ictally and interictally in partial seizures. Partial seizures can then generalize throughout their evolution to involve the hemispheres bilaterally, but, by definition, they begin confined to one hemisphere.

Both generalized and partial seizures are further classified into subtypes. There are five subtypes of generalized seizures, including: absence, myoclonic, clonic, tonic, tonic-clonic, and atonic. Each subtype has a combination of clinical and EEG findings. For

example, absence seizures typically have an abrupt onset and termination and are associated with the classic 3 Hz spike-wave complex. Partial seizures are further classified into three subtypes, simple, complex and partial seizures that evolve into a generalized seizure. Simple versus complex partial seizures are classified based on maintenance versus loss of consciousness, respectively. Simple partial seizures are then further subdivided into four categories based on symptoms: motor, sensory, autonomic, or psychic. Examples of motor symptoms include posturing, motor signs with or without march, and phonatory symptoms. Examples of sensory symptoms include all five senses with the addition of the vertiginous sensation. Autonomic symptoms can include a rising epigastric sensation, typically seen in mesial temporal lobe epilepsy, vasomotor phenomena, or mydriasis. Finally, psychic symptoms are characterized by involvement of memory, including déjà vu, changes in affect, including fear or pleasure, or other complex psychic phenomena, including illusions. Complex partial seizures can arise from simple partial seizures or evolve spontaneously. They are not subdivided based on the symptomatology. Symptomatology in complex partial seizures is characterized by automatisms, involuntary but coordinated motor activity that is purposeless and repetitive. Common automatisms include lip smacking, chewing, fidgeting, and walking. Finally, the third kind of partial seizure is that which generalizes to involve the bilateral hemispheres from either a simple or complex partial seizure.

Generalized seizures are believed to have a strong genetic component. On the other hand, partial seizures are believed to be most commonly the result of central nervous system insults. Partial seizures are the most common seizures in adults and, although the cause may never be discovered, often result from head trauma, strokes, or tumors [1].

The most common partial seizures in adults are complex partial seizures arising from the mesial temporal lobe, with hippocampal sclerosis being the most common cause of epilepsy in adults that are candidates for epilepsy surgery [2, 3]. Using recordings from intracranial depth electrodes, the ictal onset of mesial temporal lobe seizures can be localized to structures such as the hippocampus, amygdala, and adjacent parahippocampal cortex. Surgical resection of these regions of seizure foci often leads to seizure abolishment [4]. Auras are the feelings of warning sometimes experienced before a seizure occurs. Mesial temporal lobe seizures can begin with a variety of warning symptoms such as olfactory or gustatory hallucinations, an epigastric sensation, or psychic symptoms such as déjà vu or depersonalization. This represents onset as a simple partial seizure. As the seizure progresses it typically evolves into a complex partial seizure, and the patient may stare blankly, speak incoherently, or exhibit automatisms such as lip smacking or picking at clothing [5]. The ictal EEG often shows well-defined rhythmic theta seizure patterns. Often, high resolution magnetic resonance imaging (MRI) is utilized to confirm the diagnosis of mesial temporal lobe epilepsy. It has been shown that MRI is a strong predictor of favorable epilepsy neurosurgery outcome, especially if correlated with the ictal EEG [6]. Bilateral seizures and increasingly severe seizures increase the probability that there will be amnesia for the epileptic aura [7]. A study of 31 epileptic patients indicated that roughly a quarter were always aware of their seizures, over a quarter were never aware of their seizures, and the remaining half varied in whether they were aware or unaware of their seizures depending upon the episode [8].

As mentioned above, the majority of patients with nongenetic localization-related epilepsy can be controlled with medications. Epilepsy that will be refractory to medications generally presents itself in early medication trials and the chances of successful treatment with subsequent medication trials is low [9]. When epilepsy cannot be controlled with antiepileptic medications alone, the EEG-video monitoring unit is the first step in determining alternative treatments. Alternative treatment options include the ketogenic diet, vagus nerve stimulation, and epilepsy surgery.

Patients who are being evaluated for possible epilepsy surgery undergo a battery of tests to evaluate if they are eligible candidates. The location of the seizure focus can be identified by a localized EEG abnormality at the onset of the seizure, taken to be the gold standard. However, as will be discussed below, other modalities have now been shown to have increased sensitivity and specificity for identification of seizure foci. When it is not possible to identify seizure focus with scalp EEG, intracranial depth electrodes are often implanted, a much more invasive procedure.

In order to increase the sensitivity and specificity of seizure focus identification along with decreasing the invasiveness of the pre-surgical workup, several imaging modalities have been investigated. One such technique is ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), an imaging method that measures cerebral glucose uptake. Another imaging modality, ^{99m}Tc-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO) single-photon emission computed tomography (SPECT), allows researchers to observe regional cerebral blood flow changes during both ictal and interictal states. The use of cerebral blood flow to measure neuronal activity in the brain is based on the knowledge that neurons require ATP for electrical signally. ATP generation is dependent upon

glucose, which is delivered to neurons via the blood supply. SPECT imaging generates data about the relative changes in blood flow in the different regions of the brain. Coregistration of SPECT data onto MRI data allows for functional-anatomical correlation and enhances SPECT's localizing data. The use of SPECT versus PET in looking at regional brain activity ictally is of more use because of the improved time resolution in SPECT. SPECT scans reflect blood flow during a 30-60 second window, and PET reflects metabolism during a 30-45 minute window. The intravenous tracer substance, ^{99m}Tc-HMPAO, which is injected in SPECT, allows for relative ease in obtaining ictal scans. ^{99m}Tc-HMPAO crosses the blood brain barrier within 30-60 seconds after injection, binds tightly to brain tissue, and does not redistribute for 6-8 hours. Therefore, after ictal tracer injection, the patient can undergo SPECT scanning an hour or more later allowing for visualization of the regional cerebral blood flow in the ictal state [10]. Thus, this method allows for clinicians to inject tracer during a seizure and scan postictally. The same tracer can be used to obtain interictal SPECT scans. Taking the absolute values of blood flow ictally minus the interictal values generates difference images. Difference images derived from ictal/interictal SPECT comparison in combination with SPECT and MRI images as shown in Fig. 1 have been shown to increase the ability to localize seizure foci. In this study of 12 epilepsy patients, the locus was confirmed with EEG, intracranial EEG, and successful surgery [11].

As one could imagine, timing of the injection during a patient's seizure is difficult to truly standardize. It is dependent upon the staff of the ward recognizing the seizure in a timely fashion and then administering the isotope. A later study done by the same group mentioned above used SPECT difference imaging to look at the evolution and

localization of postictal blood flow changes in partial seizures. They showed hypoperfusion occurring 100 seconds after seizure termination in seizure loci. Hypoperfusion of >20% was shown to last for 30% of the time of the seizure after seizure termination, a finding that led to the hypothesis that a long seizure is accompanied by a long hypoactive phase [10]. In light of the fact that it is difficult to obtain a true ictal SPECT, further studies have been done to evaluate the sensitivity and specificity of SPECT difference analysis, as applied to the localization of seizure foci. In a study done on 53 patients, they looked at ictal and immediate post-ictal SPECT for localizing seizure foci. The study indicated that late injection (immediate post-ictal) is as sensitive but not as specific as ictal injection. However, on comparison to other more invasive methods used in localizing seizure foci, such as the gold standard EEG, SPECT perfusion difference analysis had a higher specificity and sensitivity [12]. A later study looked at the evolution of blood flow changes based on the timing of the ictal injection. This study involved 18 patients, 8 injected ictally, 5 injected immediately after seizure cessation, and 6 injected well after seizure termination. The results of the study indicated a progression from ictal hyperperfusion to excessive hypoperfusion and finally to persistent interictal hypoperfusion. As in previous studies, the period of excessive hypoperfusion appeared to last approximately one-third of the duration of the seizure. The researchers concluded that an optimal window for ictal injection should be defined because injecting just before the seizure ends may result in seeing no differences in blood flow because you may catch the transition from hyperperfusion to hypoperfusion [13]. This previous study measured perfusion based on a normalization of seizure duration determined by seizure offset. However, a later study by the same group indicated that time from onset and not

normalized time from offset should be used in analysis. In this study, 67% of patients receiving injection within 100 seconds of seizure onset demonstrated hyperperfusion at the locus while 100% of patients receiving injections more than 100 seconds after seizure onset showed hypoperfusion. The injection time from seizure offset did not reliably predict whether foci were hyperperfused or hypoperfused [14]. A study involving 11 patients with intractable partial epilepsy showed that SPECT difference imaging accurately determines seizure foci when the injection is given during the seizure, resulting in hypoperfusion, or soon after the seizure, resulting in hyperperfusion, when compared with intracranial EEG recording obtained simultaneously. The change from hyperperfusion to hypoperfusion based on timing of injection further emphasizes the need to consider injection time when interpreting SPECT difference imaging results [15]. In order to further investigate how the changes in perfusion relate to timing, 21 patients with ictal injection times were included in a study that looked at regional cerebral blood flow changes as quantified on SPECT imaging taking into account the time from seizure onset. This study indicated that, similar to postictal patients injected 90-100 seconds after seizure onset, ictal patients injected 90 seconds after seizure onset exhibit decreased cerebral blood flow in the region of the epileptogenic locus. The researchers concluded from these results that there is likely a similar metabolic mechanism underlying the similar results seen in the ictal and postictal time periods [16].

Lactate production is thought to cause the hypoperfusion in the seizure locus 90 seconds after seizure onset [17]. Lactate is involved in non-oxidative glucose metabolism, which reaches its peak around 90 seconds after seizure onset, as confirmed by microdialysis and magnetic resonance spectroscopy studies [18]. Brain lactate levels

remain elevated after seizures for up to an hour or more, and the accumulation of lactate is thought to impair autoregulation, therefore leading to hypoperfusion [19]. The results of this study further highlights the importance of looking at both increased and decreased blood flow in ictal SPECT imaging.

To examine whether the results of peri-ictal SPECT difference images are reproducible, the SPECT imaging results from thirteen patients who had two peri-ictal and at least one interictal SPECT scan were studied. In this paper, location accuracy of SPECT difference images were compared with the accuracy of interictal EEG, ictal EEG, interictal intracranial EEG, ictal intracranial EEG, MRI and PET using surgical resection site as the standard. The results of this study indicated that SPECT results were the most accurate out of all modalities and were reproducible 92% of the time compared to the accuracy if interictal EEG (46%), ictal EEG (38%), interictal intracranial EEG (44%), ictal intracranial EEG (89%), MRI (46%), and PET (69%). This study concluded that quantification of SPECT difference image results along with consideration of injection time improves diagnostic interpretation of the results and suggest that repeated SPECT scans can help confirm the location of the epileptogenic site in medically refractory epilepsy patients. Furthermore, knowledge of the presumed pathology and time of the injection may yield improved diagnostic accuracy in SPECT difference images by helping to ignore irrelevant areas of regional cerebral blood flow change [20].

Several researchers have utilized SPECT imaging in the study of epilepsy in order to analyze cerebral network activities underlying seizures. In a SPECT study involving 26 patients with generalized tonic-clonic seizures, focal cerebral blood flow increases were observed in specific brain regions. Furthermore, the bilateral frontal and parietal

association cortices were most intensely involved [21]. Another SPECT difference imaging study involving 24 patients with complex partial seizures and hippocampal sclerosis showed ictal hyperperfusion in the temporal lobe ipsilateral to the seizure focus, the border of the ipsilateral middle frontal and precentral gyrus, both occipital lobes and two small regions in the contralateral postcentral gyrus whereas hypoperfusion was seen in the frontal lobes, contralateral posterior cerebellum and ipsilateral precuneus. An association between ipsilateral temporal lobe hyperperfusion and ipsilateral frontal hypoperfusion was found along with an inverse association between seizure duration and hyperperfusion in the ipsilateral anterior cerebellum and contralateral postcentral gyrus [22]. These studies and others have investigated the neural networks that are involved during seizures. As mentioned above, partial seizures are further classified based on maintenance versus loss of consciousness into simple versus complex partial seizures. The relationship between the neuronal network involvement seen in seizures and impairment in consciousness has not previously been investigated.

In 1981, a Commission revised the classification of partial epilepsy basing simple versus complex on maintenance versus loss of consciousness. The definition of consciousness in this classification scheme is passed on patient responsiveness to exogenous stimuli [23]. The disturbance of consciousness seen in complex partial seizures is normally most notable late in the seizure and may persist for several minutes after seizure cessation. Defining consciousness has been much disputed topic by philosophers throughout the ages. Several authors have attempted to elucidate this topic in the context of epilepsy. For example, one criticism of this new classification is that it assumes normal processing during an ictal event, being able to process language and

having intact memory for recall of ictal events. As amnesia for ictal events is often used as a criteria for loss of consciousness, inadequate memory consolidation could explain ictal amnesia while other functions dependent upon maintenance of consciousness can be intact ictally such as goal-directed behavior [24].

Gloor, in a critical review of consciousness as it relates to epilepsy published in Epilepsia in 1986, purported that consciousness does not further the understanding of seizures mechanisms and brain mechanisms for theoretical and empirical reasons. He states that consciousness cannot be adequately defined, although it is open to research. Loss of consciousness may be due to aphasia, inability to perform voluntary movements, ictal or postictal amnesia, or to diversion of attention by a hallucinatory experience. He believes that amnesia is an unreliable sign of loss of consciousness because it may be absent during a seizure only to appear postictally. Gloor encourages accurate observation of seizures and interaction with patients during the seizure to attempt to distinguish loss of consciousness from other disturbances. In concluding his argument, Gloor proposes that complex partial seizures should be redefined to be partial seizures associated with a disturbance of cognitive functions. He bases this statement on his belief that an objective measurement of impairment of consciousness is not definable or analyzable in scientific terms [25].

Searle argued in his 1994 publication on this topic that consciousness and brain activity are interrelated by definition and are actually two levels of description of the same process. Consciousness is both a cause of brain processes and a function of them [26].

Zappulla's 1997 paper entitled, "Epilepsy and Consciousness," came to a different conclusion than Gloor's 1986 paper. He concluded that modeling conscious-dependent aetivity as a series of interactive parallel information channels allows the clinician to objectively measure responses that are believed to be dependent upon consciousness. This model purports that the channels ean be disrupted selectively at any stage of neural processing, leading to the behavioral patterns seen ictally. In his paper, Zapulla describes the approach of utilizing the Artificial Intelligence approach as a framework to approach mental states and consciousness. In this approach, mental states are defined as causal relations between sensory input, behavior, and other mental states. It allows mental activities such as perception, memory, and problem solving to be examined independent of any definition of eonsciousness. Using this process oriented approach, an investigator can correlate speeific cognitive processes to specialized regions of the brain. Alterations in responsiveness ictally can arise from inattention or from disruption of the attention processes. The attention process, anatomieally located in the parietal lobe, can be disassociated from the areas of the brain responsive for contents of consciousness and verbal expression, located in the anterior brain [24].

Several researchers have examined the anatomic and EEG correlates of consciousness. Porter and Penry's 1973 paper described their study of 14 patients with absence epilepsy. In this study, the first attempt to precisely evaluate a particular time point during spike-wave EEG diseharges was made through the use of a paroxysm-triggered method consisting of a modified reaction-time dèvice. This device allowed for testing of responsiveness at the exaet onset of the paroxysm. In this study, degree of spike-wave generalization appeared to be inversely related to level of responsiveness

[27]. In a study of 26 patients with absence seizures, it was shown that any spike-wave paroxysm on EEG can lead to impaired consciousness regardless of duration [28]. The reticular activating system is accepted as the system responsible for maintaining the state of wakefulness. The contents of consciousness are accepted to be a product of cortical activity. Therefore, a disturbance in the reticular activating system or in the bilateral cortex can result in an alteration in consciousness [29]. The disturbances of consciousness seen in complex partial seizures are mainly due to subcortical disturbances [30]. A study of 142 patients with partial seizures showed a correlation between bilateralization of seizure discharges and impaired consciousness. This study was done with intracranial EEG. Loss of consciousness was seen in patients with frontal lobe epilepsy in the nonlanguage dominant side and in patients with lateral temporal lobe epilepsy on the language dominant side [31].

Neuroimaging now allows for direct observation of brain activity during seizures. Utilizing neuroimaging, the topic of consciousness and its relation to partial seizures can be examined in an objective way. In doing so, attempts can be made to elucidate the network mechanisms underlying consciousness in an objective manner. Thus, this method approaches the definition of consciousness from an objective definition hopefully negating the arguments noted above regarding the uncertainty of previously used subjective measures of consciousness.

In his 1998 paper published in Epilepsia, Yamauchi defined consciousness as fulfilling the following criteria: "1. Full attention to surroundings; 2. Accurate comprehension of environment; 3. Precise memory of perceived content or experienced matter; 4. Accurate orientation to place, time, and person; 5. Prompt and appropriate

response to external stimuli [30]." Blumenfeld proposed a working model of cognitive functions in 2002 involving the complex interactions of separate sensory and motor systems receiving inputs, processing data, and generating outputs in parallel allowing for processing at multiple levels simultaneously. Based on this model, consciousness is based on three related processes: the awake, alert state, attention, and awareness of self and environment, and consciousness can be lost when content or level of consciousness is disturbed [32].

Using Blumenfeld's working model of cognitive functions and the newfound ability SPECT difference neuroimaging gives researchers to directly observe brain activity, we designed a study to attempt to identify the anatomic substrates determining maintenance versus loss of consciousness in partial epilepsy arising from the temporal lobe. In complex partial seizures, we found widespread bilateral cortical and subcortical regional cerebral blood flow changes ictally and peri-ictally. Simple partial seizures, however, caused much more localized regions of blood flow change, limited mostly to the temporal lobe. Use of correlation analysis demonstrated a strong correlation between cerebral blood flow increases in the upper brainstem and medial thalamus and cerebral blood flow decreases in higher order association cortex in complex partial seizures. Thus, our results suggest that long-range network interactions may play an important role in the loss of consciousness seen in complex partial seizures arising from the temporal lobe.

STATEMENT OF HYPOTHESIS AND PURPOSE:

The purpose of this study was to attempt to elucidate the network mechanisms underlying loss of consciousness in mesial temporal lobe epilepsy utilizing single photon emission computed tomography (SPECT). Although SPECT difference imaging has been shown to assist with seizure localization and has been studied in mesial temporal lobe epilepsy patients, this technique has not been applied to the question of the mechanisms behind loss versus maintenance of consciousness. Our aims included: to determine cerebral blood flow (CBF) changes at different times in relation to seizure occurrence, both ictally and interictally; to investigate how the changes in CBF are related to changes in behavior, specifically to the loss versus of maintenance of consciousness; to investigate whether there are correlations between regions of the brain with changes in CBF and the loss versus maintenance of consciousness. Therefore, our hypothesis was that there would be a difference in neuronal activity, as represented by changes in CBF seen in SPECT imaging, based on whether consciousness was maintained or lost, simple versus complex partial seizures, respectively, in mesial temporal lobe epilepsy. The purpose of this study is to utilize the information regarding regions of the brain and network mechanisms responsible for the loss of consciousness seen in complex partial seizures to further the understanding of consciousness in normal individuals and gather more information regarding the network mechanisms underlying loss of consciousness in complex partial seizures, with the goal of possibly preventing loss of consciousness in these patients through new treatment modalities.

METHODS:

My primary role in this study was to review, describe, and characterize ictal events on video tapes, gather and analyze clinical data including age, sex, diagnostic studies, MRI and SPECT scans, to select appropriate patients for inclusion in this study, and to then integrate, interpret, and analyze the data. SPECT SPM image analysis was done by Kelly McNally with assistance from LeBron Paige, George Zubal, Susan Vanderhill, Richard Chung and Hal Blumenfeld. Sarah Doernberg assisted in patient selection and collection of clinical data. SPECT images were acquired by the nuclear medicine staff and read with the assistance of Edward Novotny, George Zubal, and Susan Spencer. Susan Spencer, Hal Blumenfeld, and Edward Novotny assisted with interpretation of clinical information.

Patient Selection:

24 ictal-interictal SPECT images pairs from a total of 21 patients were included in this study. In order to study a relatively homogeneous group of patients, inclusion and exclusion criteria were chosen. The patients in this study all have surgically proven temporal lobe epilepsy. Consecutive patients all referred to the Yale Epilepsy Program between 1993 and 2001 were included if they fit the following criteria: ictal SPECT performed during video and scalp EEG monitoring; interictal SPECT performed at least 24 hours after the most recent seizure; verbal questions or commands were addressed to the patient during the seizure and recorded on video; combination of tests supporting left or right mesial temporal lobe seizure onset (MRI, FGD-PET, neuropsychology testing, angiogram Wada test, scalp EEG, intracranial EEG); surgical pathology demonstrating

hippocampal sclerosis; and successful surgery with no seizures during a minimal follow-up of one year following antero-medial temporal lobe resection. Patients were not included in this study if they fit any of the following criteria: significant anatomical lesion outside of the temporal lobe; prior intracranial surgery; inadequate (less than one year) follow-up; seizures which secondarily generalized; or SPECT images acquired during intracranial EEG monitoring [33]. Of the 21 patients included in this study, there were 9 males and 12 females with a mean age at the time of SPECT imaging of 25 years (range 15-57).

Patient Evaluation:

Patients were evaluated as part of the standard pre-surgical evaluation, which includes a detailed history and full neurological and general physical examination. A battery of diagnostic testing was done including high-resolution MRI scan, PET scan, ictal SPECT scan, interictal SPECT scan, continuous scalp EEG with audio-video monitoring, detailed neuropsychiatry testing, and Wada testing. A variety of clinical information was collected on each patient, including seizure localization, seizure type and duration, injection time, and surgical outcome and pathology.

Seizure type and duration were determined by video review of the seizure during which the SPECT agent was injected. Two readers, myself and another researcher reviewed all videotapes, each blinded to the results of the imaging studies. Seizure duration was determined by identifying the earliest and latest EEG or clinical evidence of seizure activity. SPECT injection time was defined as the time when the syringe plunger was fully depressed. The two readers also evaluated the patients' level of responsiveness

using a two-level classification, modified from Lee *et al.* [34]. Complex partial seizures were identified as those in which patients had impaired responsiveness to verbal questions or commands or amnesia. Simple partial seizures were identified as those in which patients remained fully alert and interactive throughout. In all patients included in this study, questions or commands were presented to the patient by medical staff or family members during the videotaped seizure.

Ictal-Interictal SPECT Study:

Ictal SPECT injections were performed during continuous scalp EEG and video recordings. At the time when the onset of a seizure is recognized, a technologist performed an intravenous injection of Tc-99m labeled hexamethylpropylene-amine-oxime (HMPAO) (Medi-Physics, Amersham Healthcare, Arlington Heights, IL, USA). This radiopharmaceutical agent enters the brain rapidly and becomes trapped within cells in proportion with cerebral blood flow. Within 60 seconds of the intravenous injection, 90% of cerebral uptake is complete [35]. The radioactive tracer binds tightly to cells allowing for accurate SPECT scans hours after injection. After at least 24 hours of no seizure activity, interictal SPECT injections were performed in these same patients.

Acquisition of SPECT images was accomplished within 90 minutes of injection. Projection data were acquired on a Picker PRISM 3000 camera (Philips Medical Systems, Best, Netherlands) and transverse slices were reconstructed as described previously [11], [36]. SPECT image data were transferred to personal computer with Linux operating system (Red Hat Software, Inc., Sterling, VA). See Fig. 2, 3.

Image Analysis:

Statistical parametric mapping (SPM99, Wellcome Department of Cognitive Neurology, London, UK hyyp://www/fil.ion.ucl.ac.uk/spm/) on a MATLAB 6.5 (The MathWorks, Inc. Natick, MA) platform was used to analyze images. SPM modules are described in detail in previous studies [37, 38] and include procedures for image coregistration, spatial normalization, and statistics calculations. To allow for group analysis of ipsilateral and contralateral changes, the images from patients with right temporal onset seizures were flipped from right to left prior to analysis. Next, the SPM realign function was used with the ictal and interictal SPECT images for each patient to create mean images. These mean images were then spatially normalized to the SPM SPECT template. The normalization parameters derived for each patient were then applied to the ictal and interictal SPECT images to normalize them to the SPM SPECT template in the SPM standard anatomical space (MNI space). Smoothing of images was accomplished using a Gaussian kernel (16 x 16 x 16 mm). Proportional scaling with an analysis threshold of 0.8 was used to normalize global intensity to correct for differences in total brain counts between ictal and interictal scans [37, 38].

A paired t-test model was used in SPM to compare the ictal versus interictal images for groups of patients. Clusters were rejected if they fell below the extent threshold (k) of 125 voxels, which is equivalent to a volume of 1cc (with SPM voxel dimensions of 2 x 2 x 2 mm). For each individual voxel threshold, the significance threshold p was 0.01, corresponding to a Z-score of 2.33. After corrections for multiple comparisons for the entire brain, clusters of voxels showing changes were identified at a significance level p=0.05.

Volumetric Analysis of SPECT Changes in Individual Patients:

By initially performing a volumetric analysis of mean percent ictal-interictal changes in anatomically defined cortical and subcortical brain regions, we were able to analyze the correlation inter-regionally. The SPM MRI template Colin27 (see http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html and ftp://ftp.mrc-cbu.cam.ac.uk/pub/imaging/Colin/) was manually segmented into 15 anatomical regions on each side of the brain using a 3-dimensional multi-modal image registration viewer written by C.S. (http://rview.colin-studholme.net/): frontal association cortex, perirolandic cortex, parietal cortex, mesial temporal cortex, lateral temporal cortex, occipital cortex, basal ganglia, medial thalamus, lateral thalamus, hypothalamus, midbrian-diencephalic junction and pretectal areas ('subthalamus"), midbrain tegmentum, midbrain substantia nigra, pontine tegmentum, and cerebellum. We then calculated the percent changes between interictal and ictal SPECT for each volumetric region in each individual patient by taking the mean of [(ictal-interictal)/interictal]x100% for all voxels in each region. Spatial normalization of SPECT images to the MRI template, and global intensity normalization of ictal and interictal images was as described above for the SPM analysis.

Correlation Analysis:

Statistical analysis of the percent changes in the identified volumes was performed using SPSS 11.5 (SPSS Inc., Chicago, Illinois). We first calculated correlation coefficients between all possible combinations of cortical and subcortical

regions on the side ipsilateral to seizure onset. Principal components analysis was next used to identify groupings of related variables. Three components were identified based on concordance of both the Cattell scree test and the Kaiser rule, retaining only components with eigenvalues >1.0 without rotations [39].

Based on these analyses, we selected the medial thalamus ipsilateral to seizure onset as a crucial node with high positive and negative correlations to numerous cortical and subcortical structures. We then performed an SPM analysis using the multi-subject, conditions and variates model, entering the ictal-interictal percent change in the medial thalamus ipsilateral to seizure onset as the covariate. This generated a t-map of the partial correlation b between the medial thalamic changes and changes in all other brain regions between interictal and ictal scans. For this analysis, we again used an extent threshold k = 125 voxels, voxel-level significance threshold p = 0.01, followed by a cluster-level significance level p=0.05 corrected for multiple comparisons for the entire brain.

RESULTS:

Clinical Features:

Clinical information for each subject is presented in Table 1. There were 18 patients included in the analysis with complex partial seizures and 6 patients with simple partial seizures.

Complex Partial Seizures:

The SPECT images from the patients with complex partial seizures were analyzed during two time epochs, at 60-90s after seizure onset, or >90s after seizures onset (see Fig. 4, 5, 6). The reasoning behind choosing seizure onset versus end in defining these patients group is that onset can be more precisely determined based on EEG and behavior than seizure end. The mean seizure duration was approximately 90s, which led to our choice of 90s as the injection time cut-off. For the 60s-90s group (n=8), the mean seizure duration was 94 ± 17.7s (mean ± SEM) and mean injection time after seizure onset was 73 ± 8.9s. For the >90s group (n=10), the mean seizure duration was 91 ± 21.8s and mean injection time after seizure onset was 130 ± 10.1s. Therefore, the 60-90s group consists of patients injected about 30s before the end of the seizure (28 ± 21.4s), which represents the late ictal period. In the >90s group, the patients were injected about 40s after seizure termination (40 ± 13.4s), which represents the early post-ictal period.

As can be seen in Figure 4, complex partial seizures were associated with functional imaging changes in widespread cortical and subcortical networks. The most significant cerebral blood flow increases in the 60-90s group were present in the temporal

lobe of seizure onset, maximal in the anterior, or pes hippocampus (Fig. 4a, 5; Table 2). More minor increases were present in other ipsilateral and contralateral neocortical areas but did not reach statistical significance at the cluster level. In the 60-90s group, significant subcortical increases were present in the ventral basal ganglia on the side of seizure onset, particularly in the region of the ventral pallidum (Fig. 5b,c).

Also significant were the cerebral blood flow decreases seen during the complex partial seizure patients in the 60-90s group in the bilateral orbitofrontal, anterior cingulated, lateral frontal, and parietal association cortex, but of slightly greater magnitude on the side of seizure onset (Fig. 4a, Table 2). Relatively spared of these changes were the primary cortical regions including the primary auditory, primary visual, and perirolandic cortices.

In the patients with complex partial seizures in the >90s group, which, as mentioned above, represents the early post-ictal period, the temporal lobe is no longer activated (Fig. 4b). However, marked increases do occur in this group in various subcortical structures known to have limbic connections. These included the bilateral medial thalamus, hypothalamus, subthalamus (midbrain-diencephalic junction), midbrain, and upper pone (Fig. 4b, Fig. 6, Table 2). The bilateral cerebellar vermis also is activated.

In the >90s group, similar to the 60-90s group, marked cerebral blood flow decreases persist in the bilateral higher order association cortex, including the orbitofrontal, anterior cingulated, lateral frontal, and parietal cortex, with slightly greater magnitude on the side of seizure onset (Fig. 4b, Fig. 3, Table 2).

Simple Partial Seizures:

The SPECT images from the patients with simple partial seizures (n=6) were also analyzed. The injection times in these 6 patients were very similar to the 60-90s complex partial group (78 vs 73s). The mean injection time after seizure onset in the patients with simple complex seizures was 78 ± 6.7s and the mean time from the end of the seizure until the injection was 11 ± 17.1s. The seizure durations were slightly shorter in the simplex partial seizure group (67 vs 97s), although not significantly so (p=0.32, two tailed t-test). In a prior study, individual patients in the simple partial group analyzed by SPECT difference imaging [11, 36] showed focal cerebral blood flow increases in the temporal lobe either on the side of seizure onset, or bilaterally in 5 of 6 patients. However, due to individual variations in the anatomic locations and magnitude of these changes, the group data showed only small increases in the contralateral temporal lobe and cerebral peduncle, none of which reached statistical significance at the cluster level (Fig. 7). Notably, the widespread bilateral cerebral blood flow decreases seen in the higher order association cortex with complex partial seizures (Fig. 4) were strikingly absent in the simple partial seizures, both in the individual (not shown) and group data (Fig. 7).

Network Connections:

In order to investigate a possible mechanism for the hypoperfusion seen in the frontal and parietal association cortex during complex partial seizures, we divided the brain into anatomical regions and calculated the Pearson correlation between perfusion

changes in each region and all the others ipsilateral to seizure onset (Table 3). In doing this analysis, we used the ictal-interictal SPECT scan pairs from all temporal lobe patients at all injection time included in this study (n=24). Several clear trends can be seen when using this exploratory method after roughly correcting for multiple comparisons by increasing the significance threshold to 0.001 (Table 3). A strong positive correlation was seen between several of the midline subcortical structures including the medial thalamus, lateral thalamus, subthalamus, hypothalamus, midbrain tegmentum, midbrain substantia nigra, and pontine tegmentum. This finding suggests that changes in these structures tend to occur in the same direction. Also of note, there was a strong negative correlation between changes in the frontal and parietal cortex and these subcortical structures, especially the medial thalamus ($p<0.001$, $p=0.008$ for the frontal and parietal cortex, respectively). Also seen was a strong positive correlation between the frontal and parietal cortex ($p=0.001$, Table 3). These findings imply an inverse relationship may exist between changes in perfusion in the midline subcortical structures and the association cortex during temporal lobe seizures. On the other hand, the changes in the mesial and lateral temporal lobes were not correlated with changes in the association cortex. Perfusion changes in the mesial and lateral temporal lobes were strongly positively correlated with the changes in cerebral blood flow seen in the ipsilateral basal ganglia ($p<0.001$), (Table 3). This finding has previously been related to dystonic limb movements during temporal lobe seizures [40].

In order to identify groupings of related variables with a more rigorous method, we next applied principal components analysis to the same data set. Three principal components were identified based on the Cattell scree test and the Kaiser rule [39],

representing three groupings of highly inter-correlated brain regions, which accounted for 78% of the total variance in the data. Variables with the greatest factor loading in each component are most highly inter-correlated, and in descending order for each component were as follows: First component, positive factor loading – subthalamus, medial thalamus, midbrain substantia nigra, midbrain tegmentum, lateral thalamus, pons, and hypothalamus; first component negative factor loading – frontal and parietal. Second component, positive factor loading – lateral temporal, medial temporal, basal ganglia, and occipital. Third component – positive factor loading – parietal and frontal. Thus, the principal components analysis confirmed the findings based on identification of highly correlated regions (Table 3). These results are summarized in Fig. 8. Midline subcortical structures from one network of strong positive correlations, while the frontal and parietal cortices form a second network of positive correlations (Fig. 8a). These cortical-subcortial networks appear to interact through negative correlations via the thalamus (Fig. 8a,c,d). Another network of positive correlations is formed by the temporal lobe and basal ganglia (Fig. 8b, e).

Based on the above findings, we chose the medial thalamus ipsilateral to seizure onset as a crucial node with high positive and negative correlations to numerous cortical and subcortical structures. SPM enables analysis of data for the entire brain with correction for multiple comparisons in the entire analysis volume [37, 38]. We therefore performed an SPM analysis of the partial correlation between medial thalamic changes ipsilateral to seizure onset and changes in all other brain regions bilaterally (fig 9). Using this approach, we found significant positive correlation between the ipsilateral medial thalamus, and the ipsilateral thalamus, subthalamus, and midbrain, as well as the

contralateral medial thalamus (cluster-level p=0.001 corrected for multiple comparisons, k=1894, maximum voxel Z=6.71). A smaller region of significant correlation was also present with the ipsilateral medial cerebellum (p=0.015, k=873, Z=3.98). Significant negative correlation was found between the ipsilateral medial thalamus and the bilateral orbital frontal, ipsilateral lateral frontal and parietal, and the contralateral temporal cortex (p=0.000, k=16, 900, Z=5.44). This more statistically robust approach confirms that changes in the medial thalamic perfusion in temporal lobe seizures are positively correlated with ipsilateral midline subcortical structures, as well as with the contralateral medial thalamus, and are negatively correlated with bilateral regions of the association cortex.

DISCUSSION:

Through the use of relatively new imaging technology, our study examines the network connections, which may underlie the loss of consciousness seen in complex partial seizures. Consciousness and epilepsy has been a long disputed topic explored from a philosophical and qualitative manner in the past. SPECT ictal-interictal difference imaging has been shown to have high sensitivity and specificity for detecting seizure foci and is now accepted as a method to examine changes in neuronal activity that occur ictally. In applying SPECT difference imaging techniques to the scientific query of what network connections underlie loss of consciousness in complex partial seizures, we were able to quantitatively assess changes in neuronal activity and develop a possible hypothesis for the network connections behind the changes in consciousness seen in epilepsy patients.

The results of this study showed widespread changes in cerebral blood flow in the cortical and subcortical regions of the brain of patients with complex partial temporal lobe seizures. When compared with simple partial seizures, in which there were more limited changes in the temporal lobes, there is a significant difference. Complex partial seizures were associated with marked decreases in blood flow in regions of the association cortices bilaterally with more profound changes on the side ipsilateral to seizure onset. The areas of decreased blood flow included the lateral prefrontal, anterior, cingulated, orbital frontal, and lateral parietal cortex.

These results lend further support to the "network inhibition hypothesis" recently proposed by researchers in our group in which the idea that complex partial temporal lobe seizures propagate to the medial thalamus and upper brainstem reticular formation,

thereby disrupting the normal neuronal activating functions [41] (Fig. 10). This hypothesis could explain the results of our current study with increases in blood flow seen subcortically and decreases seen in the bilateral frontal and parietal association cortices. The excitation subcortically with subsequent disruption of normal neuronal activating functions may lead to a functional inactivation, or abnormal inhibition, of the association cortices resulting in the decrease in blood flow. Several mechanisms, including synaptic depression [42], activation of inhibitory neuronal pools, spreading depression [43], and depolarization block [44, 45], have been shown to cause decreased activity in regions connected via synapses to regions with abnormally increased neuronal activity. This concept of "surround inhibition" is not a new one and has been reported in both animal studies [46-49] and human studies [50-55] that utilized electrophysiological, metabolic, and neuroimaging techniques. For example, intracranial EEG studies have shown slow waves in the frontal cortex during temporal lobe seizures, thought to represent cortical inhibition [56, 57]. Several researchers have proposed the hypothesis that these regions of inhibition outside of the seizure focus serve to prevent seizure spread and thus have an adaptive function [22, 55]. This hypothesis is supported by the fact that temporal lobe seizures usually do not generalize and remain confined to the limbic cortex.

One possible critique of our hypothesis that the decreases seen in the frontal and parietal association cortices are secondary to an inhibitory phenomena arising subcortically is that the changes in blood supply are actually due to a vascular steal phenomenon. However, this is unlikely because of the blood supply in the brain. The posterior circulation supplies blood to the midline subcortical regions while the anterior

and middle cerebral arteries, both part of the anterior circulation, provide the blood supply to the frontal and parietal association cortices. In addition, some regions, including the peri-Rolandic cortex of the middle cerebral artery territory, were almost entirely spared from the hypoperfusion phenomena seen in other regions supplied by the same artery. Furthermore, there was no significant correlation between the amounts of increased blood flow subcortically and the amount of decreased blood flow in the fronto-parietal association cortex (Table 3).

Another possible critique of our hypothesis is that a vasoconstriction phenomena similar to that seen in migraines is causing the hypoperfusion in the fronto-parietal association cortices triggered by the ictal discharge. As post-ictal migraine is a well-known entity, further research is necessary to negate this alternative hypothesis for the changes in blood flow we observed in this study.

Several recent works from our group lends further support to our hypothesis and raises interesting questions. In a study completed by our group and recently submitted for publication, 31 intracranial EEG recordings in 11 patients with mesial temporal lobe epilepsy and hippocampal sclerosis were examined. The EEG results support the SPECT difference imaging results detailed in this paper. Increased EEG activity was seen in the mesial and lateral temporal regions ipsilateral to seizure onset. Most interestingly, there was prominent irregular slowing, termed "sleep-like ictal neocortical slowing," seen in the bilateral frontal and ipsilateral parietal association cortex during and following temporal lobe seizures [58]. In another study, SPECT ictal-interictal difference imaging was used to look at patients with generalized tonic-clonic seizures. This study, similar to the work presented in this paper, showed focal blood flow changes. However, the

increases were seen in the bilateral frontal and parietal association cortices, the opposite finding that we saw in partial seizures arising from temporal lobe foci [59]. The results of these studies could suggest that abnormal activity in the fronto-parietal cortex may lead to loss of consciousness either through abnormal relative increases or decreases in neuronal activity (see Fig. 11).

In conclusion, the results of this study suggest that in partial seizures arising from foci in the temporal lobe there are increases in cerebral blood flow due to relative increases in neuronal activity early in the seizures. In addition, simple partial seizures, in which patients maintain consciousness, do not exhibit physiologic changes outside of the temporal lobes, whereas complex partial seizures, in which patients lose consciousness, exhibit abnormal excitatory and inhibitory activity outside the temporal lobe. Most significantly, there is an abnormal inhibition seen in the fronto-parietal association cortex seen in complex partial seizures but not in simple partial seizures.

The results of this study and the utilization of relatively new quantifiable techniques to evaluate the changes in consciousness seen in seizures open up a new angle to look at the long debated issue of consciousness. In using these techniques, the problem can be approached from a more scientific perspective instead of a philosophical one, as it has been in the past. The possibility of uncovering that the neuronal networks underlie the complex phenomena that defines one's consciousness is an exciting one. There are many feasible future studies that may help elucidate these pathways. Notably, this study only included temporal lobe epilepsy patients with partial seizures. Looking at groups of patients with extra-temporal lobe seizure foci may give further information regarding the involved neuronal pathways. Another exciting possibility for future

research is the application of functional studies. Also, as mentioned above, correlating EEG data with SPECT data may lend further support to our hypothesis. Finally, animal studies may be of use to investigate specific neurotransmitters involved in the process of inhibiting the association cortices. However, there is no doubt that as the mystery of consciousness is gradually explored there will be a multitude of additional research questions and modalities to further explore and discover. In solving this mystery, researchers cannot only help to answer long-standing questions regarding consciousness, but they can apply the newfound knowledge to the treatment of epilepsy patients and patients with other neurological disorders. For example, if one knew what regions of the brain were responsible for loss of consciousness in complex partial seizures, perhaps a treatment could halt the changes in those regions before any loss of consciousness occurred. There are numerous potential treatment advances that could be imagined if we knew more about the network mechanisms of epilepsy, all with the potential to significantly improve many patients' lives.

REFERENCES:

1. Sander, J.W., *The epidemiology of epilepsy revisited.* Curr Opin Neurol, 2003. 16(2): p. 165-70.
2. Benbadis, S., *Epileptic seizures and syndromes.* Neurol Clin, 2001. 19: p. 251-70.
3. Engel, J., *Mesial temporal lobe epilepsy: what have we learned?* Neuroscientist, 2001. 7: p. 340-52.
4. Kim, D.S., *Surgery for mesial temporal sclerosis.* Second ed. Epilepsy surgery, ed. C.Y. Luders HO. 2001, Philadelphia: Lippincott Williams & Wilkins. 643-52.
5. French, J.A., et al., *Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination.* Annals of Neurology, 1993. 34(6): p. 774-80.
6. Garcia, P.A., et al., *Prognostic value of qualitative magnetic resonance imaging hippocampal abnormalities in patients undergoing temporal lobectomy for medically refractory seizures, abstract.* Epilepsia, 1994. 35: p. 520-524.
7. Schulz, R., et al., *Amnesia of the epileptic aura.* Neurology, 1995. 45: p. 231-235.
8. Blum, D.E., et al., *Patient awareness of seizures.* Neurology, 1996. 47: p. 260-264.
9. Kwan, P. and M.J. Brodie, *Early identification of refractory epilepsy, abstract.* New Eng J Med, 2000. 342: p. 314-319.
10. Spanaki, M.V., et al., *Evolution and Localization of Postictal Blood Flow Changes in Partial Seizures Demonstrated by SPECT: Use of Quantitative Difference Images.* Journal of Epilepsy, 1998. 11: p. 25-33.
11. Zubal, I.G., et al., *Difference images calculated from ictal and interictal technetium-99m-HMPAO SPECT scans of epilepsy.* Journal of Nuclear Medicine, 1995. 36(4): p. 684-9.
12. Spanaki, M.V., et al., *Sensitivity and specificity of quantitative difference SPECT analysis in seizure localization.* Journal of Nuclear Medicine, 1999. 40(5): p. 730-6.
13. Zubal, I.G., et al., *Influence of technetium-99m-hexamethylpropylene amine oxime injection time on single-photon emission tomography perfusion changes in epilepsy.* European Journal of Nuclear Medicine, 1999. 26(1): p. 12-7.
14. Avery, R.A., et al., *Effect of injection time on postictal SPET perfusion changes in medically refractory epilepsy.* European Journal of Nuclear Medicine, 1999. 26(8): p. 830-6.
15. Spanaki, M.V., et al., *Periictal SPECT localization verified by simultaneous intracranial EEG.* Epilepsia, 1999. 40(3): p. 267-74.
16. Avery, R.A., et al., *Decreased cerebral blood flow during seizures with ictal SPECT injections.* Epilepsy Research, 2000. 40(1): p. 53-61.
17. During, M.J., et al., *Direct Measurement of extracellular lactate in the human hippocampus during spontaneous seizures.* Journal of Neurochem, 1994. 62: p. 2356-2361.

18. Cendes, F., et al., *Proton magnetic resonance spectroscopic imaging for discrimination of absence and complex partial seizures.* Annuals of Neurology, 1997. 41: p. 74-81.
19. Petroff, O.A., et al., *Cerebral lactate turnover after electroshock: in vivo measurements by 1H/13C magnetic resonance spectroscopy.* Journal of Cerebral Blood Flow & Metabolism, 1992. 12(6): p. 1022-9.
20. Avery, R.A., et al., *Reproducibility of serial peri-ictal single-photon emission tomography difference images in epilepsy patients undergoing surgical resection.* European Journal of Nuclear Medicine, 2000. 27(1): p. 50-5.
21. Blumenfeld , H. and J. Taylor, *Why do seizures cause loss of consciousness?* The Neuroscientist, 2003. 9(5).
22. Van Paesschen, W., et al., *SPECT perfusion changes during complex partial seizures in patients with hippocampal sclerosis.* Brain, 2003. 126(5): p. 1103-11.
23. ILAE, *Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy.* Epilepsia, 1981. 22(4): p. 489-501.
24. Zapulla, R., *Epilepsy and Consciousness.* Seminars in Neurology, 1997. 17(2): p. 113-119.
25. Gloor, P., *Consciousness as a Neurological Concept in Epileptology: A Critical Review.* Epilepsia, 1986. 27(2): p. S14-S26.
26. Searle, J.R., *The rediscovery of the mind.* 1994, Cambridge: MIT Press. 111-26.
27. Porter, R.J. and J.K. Penry, *Responsiveness at the Onset of Spike-Wave Bursts.* Electroencephalogr Clin Neurophysiol, 1973. 34: p. 239-245.
28. Browne, T.R., et al., *Responsiveness before, during and after spike-wave paroxysms.* Neurology, 1974. 24(7): p. 659-665.
29. Plum, F. and J.B. Posner, *The diagnosis of stupor and coma.* Ed. 3. ed. Contemporary neurology series ; 19. 1980, Philadelphia: Davis. xiii, 373.
30. Yamauchi, T., *Impairment of consciousness during epileptic seizures with special reference to neuronal mechanisms.* Epilepsia, 1998. 39(Supplement 5): p. 16-20.
31. Inoue, Y. and T. Mihara, *Awareness and responsiveness during partial seizures.* Epilepsia, 1998. 39(Supplement 5): p. 7-10.
32. Blumenfeld, H., *Neuroanatomy through Clinical Cases.* 2002, Sunderland, MA: Sinauer Assoc. Publ., Inc.
33. Studholme, C., et al., *Estimating tissue deformation between functional images induced by intracranial electrode implantation using anatomical MRI.* Neuroimage, 2001. 13(4): p. 561-76.
34. Lee, K.H., et al., *Pathophysiology of altered consciousness during seizures: Subtraction SPECT study.* Neurology, 2002. 59: p. 841-846.
35. Anderson, A.R., *99mTc-D,L-hexamthylene-propyleneamine oxime (99mTc-HMPAO): basic kinetic studies of a tracer of cerebral blood flow.* Cerebrovascular & Brain Metabolism Reviews, 1989. 1: p. 288-318.

36. Chang, D.J., et al., *Comparison of Statistical Parametric Mapping and SPECT Difference Imaging in Patients with Temporal Lobe Epilepsy.* Epilepsia, 2002. 43(1): p. 68-74.
37. Friston, K.J., et al., *Detecting activations in PET and fMRI: levels of inference and power.* Neuroimage, 1996. 4(3 Pt 1): p. 223-35.
38. Acton, P.D. and K.J. Friston, *Statistical parametric mapping in functional neuroimaging: beyond PET and fMRI activation studies.* European Journal of Nuclear Medicine, 1998. 25(7): p. 663-7.
39. Tabachnick, B.G. and L.S. Fidell, *Using Multivariate Statistics, 2nd Ed.* 1989, New York: HarperCollinsPublishers, Inc.
40. Newton, M.R., et al., *Dystonia, clinical lateralization, and regional blood flow changes in temporal lobe seizures.* Neurology, 1992. 42(2): p. 371-377.
41. Norden, A.D. and H. Blumenfeld, *The Role of Subcortical Structures in Human Epilepsy.* Epilepsy & Behavior, 2002. 3(3): p. 219-231.
42. O'Donovan, M.J. and J. Rinzel, *Synaptic depression: a dynamic regulator of synaptic communication with varied functional roles.* Trends Neurosci, 1997. 20(10): p. 431-3.
43. Somjen, G.G., *Mechanisms of spreading depression and hypoxic spreading depression-like depolarization.* Physiol Rev, 2001. 81(3): p. 1065-96.
44. Grace, A.A., et al., *Dopamine-cell depolarization block as a model for the therapeutic actions of antipsychotic drugs.* Trends Neurosci, 1997. 20(1): p. 31-7.
45. Benazzouz, A. and M. Hallett, *Mechanism of action of deep brain stimulation.* Neurology, 2000. 55(12 Suppl 6): p. S13-S16.
46. VanLandingham, K.E. and E.W. Lothman, *Self-sustaining limbic status epilepticus. II. Role of hippocampal commissures in metabolic responses.* Neurology, 1991. 41(12): p. 1950-7.
47. Ostrand, G.V. and R.M. Cooper, *[14C]2-Deoxyglucose autoradiographic technique provides a metabolic signature of cobolt-induced focal epileptogenesis.* Epilepsia, 1994. 35(5): p. 939-949.
48. Redecker, C., et al., *Coupling of cortical and thalamic metabolism in experimentally induced visual and somatosensory focal epilepsy.* Epilepsy Res, 1997. 27(2): p. 127-137.
49. Bruehl, C., et al., *Thalamocortical circuits causing remote hypometabolism during focal interictal epilepsy.* Epilepsy Res, 1998. 32(3): p. 379-387.
50. Prince, D.A. and B.J. Wilder, *Control mechanisms in cortical epileptogenic foci. "Surround" inhibition.* Archives of Neurology, 1967. 16(2): p. 194-202.
51. Collins, R.C., *Use of cortical circuits during focal penicillin seizures: an autoradiographic study with [14C]deoxyglucose.* Brain Research, 1978. 150(3): p. 487-501.
52. Engel, J., Jr., et al., *Local cerebral metabolism during partial seizures.* Neurology, 1983. 33(4): p. 400-13.
53. Handforth, A. and R.F. Ackermann, *Functional [^{14}C]2-deoxyglucose mapping of progressive states of status epilepticus induced by amygdala stimulation in rat.* Brain Res, 1988. 460(1): p. 96-102.

54. VanLandingham, K.E. and E.W. Lothman, *Self-sustaining limbic status epilepticus. I. Acute and chronic cerebral metabolic studies: limbic hypermetabolism and neocortical hypometabolism.* Neurology, 1991. 41(12): p. 1942-1949.
55. Schwartz, T.H. and T. Bonhoeffer, *In vivo optical mapping of epileptic foci and surround inhibition in ferret cerebral cortex.* Nature Medicine, 2001. 7(9): p. 1063-7.
56. Lieb, J.P., R.B. Dasheiff, and J. Engel Jr., *Role of the frontal lobes in the propagation of mesial temporal lobe seizures.* Epilepsia, 1991. 32(6): p. 822-37.
57. Mayanagi, Y., E. Watanabe, and Y. Kaneko, *Mesial temporal lobe epilepsy: clinical features and seizure mechanism.* Epilepsia, 1996. 37 Suppl 3: p. 57-60.
58. Blumenfeld , H., et al., *Sleep-like ictal neocortical slowing in temporal lobe epilepsy: A human intracranial EEG study.* submitted, 2003.
59. Blumenfeld, H., et al., *Selective frontal, parietal and temporal networks in generalized seizures.* Neuroimage, 2003. 19: p. 1556-1566.

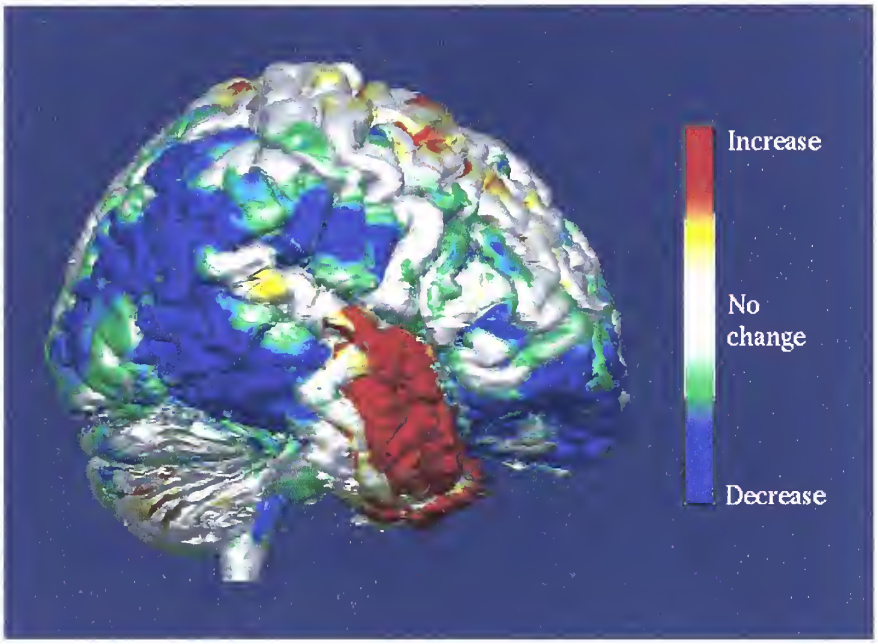

Figure 1: This image represents a three-dimensional MRI reconstruction of one patient's brain. The SPECT difference image is super-imposed on the MRI with red areas representing ictal hyperperfusion and blue areas ictal hypoperfusion. This ictal SPECT scan was obtained during a temporal lobe seizure causing the hyperperfusion in the temporal lobe.

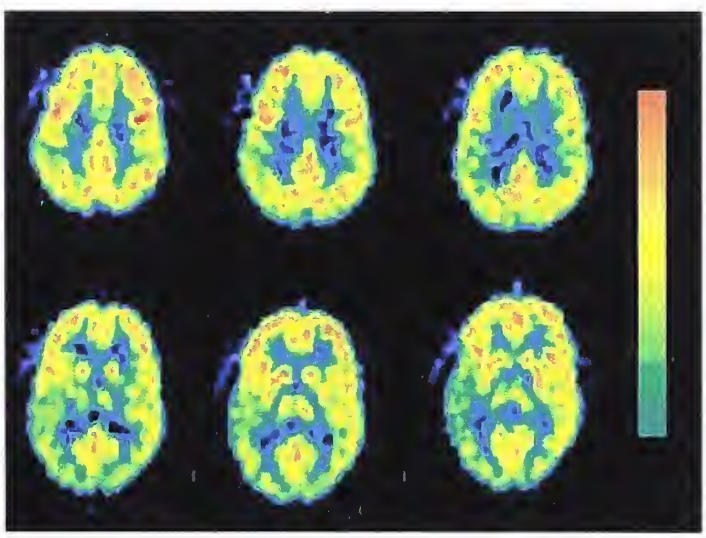

Figure 2: Raw SPECT images have this appearance prior to normalization. The scale on the right indicates magnitude of perfusion; red areas are highly perfused, whereas blue areas receive minimal blood flow.

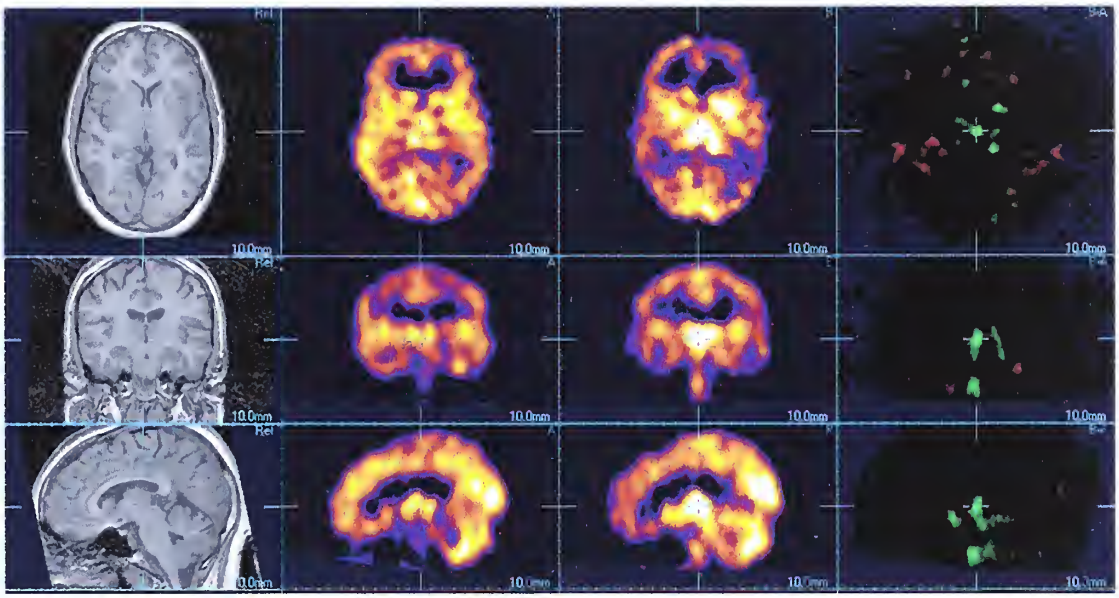

Figure 3: Typical Rview layout with an MRI scan, interictal SPECT scan, ictal SPECT scan, and SPECT difference image (from left to right). The two SPECT scans are normalized to account for global differences in tracer uptake, and the MRI and SPECT scans are aligned in three-dimensional space.

RESULTS

Patient	Seizure onset Localization	Seizure Type	Seizure Duration (seconds)	Injection Time (Relative to seizure onset, seconds)	PET confirmatory reading	MRI confirmatory reading	Ictal EEG onset	Surgical pathology	Surgical outcome
1	Left hippocampus (HC)	Complex partial seizure (CPS)	120	150	Left temporal (LT) hypometabolism	Left hippocampal (HC) atrophy	Bilateral mild irregular slowing	Left HC sclerosis	Seizure-free
2	LT	CPS	79	63	LT medial hypometabolism	Left HC atrophy	LT 5 Hz rhythmic activity	Left HC sclerosis	Seizure-free, no aura, requires antiepileptic drug (AED)
3	Right temporal (RT)	CPS	123	158	RT medial hypometabolism	Normal	RT 4-5 Hz rhythmic activity	Hippocampus with gliosis	Seizure-free
4	Left mesial temporal (MT) lobe	Simple partial seizure (SPS)	48	56	decrease LT (also smaller)	L MT sclerosis, also unilateral hemi-atrophy	L irregular slowing	HC selerosis	Seizure-free, no aura, requires AED
5A	Right HC	CPS versus SPS	188	61	Minimal R frontoparietal hypometabolism	R temporo-parietal atrophy	R temporal theta	Increased number of glial cells in white matter; Hippocampus w/no significant neuronal loss	Seizure-free, no aura, requires AED
5B	Right HC	CPS vs. SPS	145	130	Minimal R frontoparietal hypometabolism	R temporo-parietal atrophy	R temporal theta	Increased number of glial cells in white matter; Hippocampus w/no significant neuronal loss	Seizure-free, no aura, requires AED
6	Right greater than LT	CPS	61	76	subtle decrease RT metabolism	R HC atrophy and increased signal	Bilateral 3 Hz delta evolving to LT 6 Hz theta after 20sec	HC sclerosis	Seizure-free
7	Right HC	SPS	153	84	RT hypometabolism	R HC atrophy and increased signal	No changes	Cerebral cortex and white matter showing white matter gliosis and rare neurons in the molecular layer; HC sclerosis	Seizure-free, no aura, requires AED
8	Left entorhinal cortex	CPS	55	91	entire LT hypometabolism extending to Occipital	L hemi-atrophy, L MT sclerosis	diffuse L hemisphere delta evolving to LT theta	HC sclerosis	Seizure-free, no aura, requires AED
9	RT	CPS	95	72	RT hypometabolism	R HC atrophy	RT 7 Hz rhythmic theta	HC sclerosis	Seizure-free, no aura, requires AED

10	R MT lobe	SPS	45	74	decrease metabolism R temporal lobe	R MT sclerosis	R temporal theta	Increase in number of white matter glial cells in amygdala and temporal lobe, mild HC neuronal loss	Seizure-free, no aura, requires AED
11	RT	CPS versus SPS	62	86	Decreased uptake of radiotracer in the right temporal lobe, most prominent in the medial and inferior aspects of the temporal lobe	R MT sclerosis	RT 6 Hz rhythmic activity	HC sclerosis	Seizure-free, no aura, requires AED
12	L>RT (PhIII had 8 szs, 6 L mT, 2 R T (1 medial, 1 posterior); SPECT showed increase RT	CPS	118	162	LT and occipital hypometabolism	L HC atrophy and signal change	Early EEG non-localizing; ~60 seconds into seizure see RT theta	HC sclerosis	1 Isolated Seizure/Aura Activity (Requires Antiepileptic Medication)
13	R MT	SPS	36; 51	67; 69	R MT hypometabolism	R amygdala parahippocampal gyrus hippo increase T2 decrease T1 c/w consistent with glioma	Mild diffuse slowing; no EEG changes	ganglioglioma of HC with no significant neuronal loss; heterotropia of gray matter in parahippocampal gyrus	Seizure-free, no aura, requires AED
15	R MT	SPS	79	105	R medial temporal decreases	R MT sclerosis	RT irregular low amplitude slowing	HC sclerosis	Seizure-free
16A	LT	CPS	68	80	L medial temporal hypometabolism	L HC atrophy and increased T2 signal	Diffuse L hemisphere rhythmic 5-6 Hz activity	HC Sclerosis, Temporal lobe: cerebral tissue with occasional heteroopic neurons in molecular layer and glial cell proliferation in white matter	Seizure-free, no aura, requires AED
16B	LT	CPS	36	108	L medial temporal hypometabolism	L HC atrophy and increased T2 signal	Bilateral subtle irregular 3-4 Hz slowing	HC Sclerosis; Temporal lobe: cerebral tissue with occasional heteroopic neurons in molecular layer and glial cell proliferation in white matter	Seizure-free, no aura, requires AED
16C	LT	CPS	26	79	L medial temporal hypometabolism	L HC atrophy and increased T2 signal	No EEG changes	HC Sclerosis; TL: occasional heterotopic neurons in molecular layer and glial cell proliferation in white matter	Seizure-free, no aura, requires AED

17	R medial temporal	CPS	55	107	dramatic RT hypometabolism	R HC atrophy and increased T2 signal	RT 6 Hz rhythmic theta	Increased number of glial cells in white matter; HC Sclerosis	Isolated seizure
18	R HC	CPS	46	81	R anterior T extending to frontal hypometabolism	subtle R MT sclerosis	RT delta evolving to theta	White matter w/mild increase of glial cells; Cerebral tissue w/focal hemorrhage; HC Sclerosis	Marked Decrease in Seizure Activity (1generalized tonic clonic/month); Deceased
19	R medial T	CPS versus SPS	103	123	RT hypometabolism	R MT sclerosis	6-7 Hz RT rhythmic theta	HC sclerosis. White matter with moderate glial proliferation	Seizure-free, no aura, requires AED
20	LT	CPS	66	184	Normal	L HC signal abnormality but no atrophy	bilateral fronto-temporal irregular 5-6 Hz rhythmic theta	HC with pyramidal cell loss and gliosis	Seizure-free
21	LT	CPS	100	91	Marked LT hypometabolism	L HC atrophy and increased T2 signal	LT 6 Hz theta	HC sclerosis	Seizure-free, no aura, requires AED

Table 1: Relevant clinical information for the 21 study subjects. Note that a total of 24 ictal SPECT scans were obtained in the 21 study subjects. Patients 5 and 16 had multiple scans.

Table 2. Brain regions with significant changes during temporal lobe seizures

Brain regions (voxel clusters)	Cluster Significance (p)	Cluster Volume (k)	Maximum voxel location	x, y, z	Maximum voxel Z
Complex Partial Seizures 60-90 s					
Hyperperfusion:					
Ipsilateral temporal lobe, ipsilateral basal ganglia	0.000	4544	Ipsilateral pes hippocampi	-26, -8, -24	4.38
Hypoperfusion:					
Bilateral medial and orbital frontal, ipsilateral lateral frontal, contralateral insula, contralateral temporal	0.000	19488	Contralateral orbital frontal	14, 16, -14	4.22
Ipsilateral medial and lateral parietal	0.000	8298	Ipsilateral precuneus	-6, -46, 32	3.93
Complex Partial Seizures >90 s					
Hyperperfusion:					
Bilateral medial thalamus, hypothalamus, subthalamus, midbrain, pons, medial cerebellum	0.000	6555	Bilateral hypothalamus	2, -6, -12	4.49
Hypoperfusion:					
Bilateral medial and orbital frontal, ipsilateral lateral frontal, ipsilateral medial parietal, contralateral insula, contralateral temporal	0.000	27717	Contralateral insula	44, 16, -2	4.90

Same data as in Figure 4. p = cluster-level significance corrected for multiple comparisons for the entire brain. Only clusters with cluster-level significance $p<0.05$ are listed. k = cluster size in voxels (voxel size = 2x2x2 mm). x,y,z are coordinates in MNI space of the voxel with maximum Z-score for the cluster.

	Rolandic	Occipital	Lat Temp	Mes Temp	BG	Cerebell	Parietal	Frontal	Pons	SN	Mid Teg	Subthal	Lat Thal	Hypothal
Med Thal	-.379 .068	.019 .930	.293 .165	.188 .378	.323 .123	.454 .026	-.531 .008	-.674 <.001	.586 .003	.673 <.001	.700 <.001	.847 <.001	.872 <.001	.557 .005
Hypothal	-.251 .237	-.281 .183	-.060 .781	.035 .870	-.004 .984	.245 .249	-.343 .100	-.562 .004	.595 .002	.747 <.001	.632 .001	.666 <.001	.398 .054	
Lat Thal	-.362 .082	.163 .446	.505 .012	.405 .050	.519 .009	.343 .100	-.349 .094	-.638 .001	.494 .014	.665 <.001	.680 <.001	.768 <.001		
Subthal	-.300 .154	-.150 .486	.295 .162	-.430 .036	.255 .229	.310 .140	-.430 .036	-.516 .010	.614 .001	.896 <.001	.929 <.001			
Mid Teg	-.361 .083	-.074 .732	.357 .087	.190 .374	.280 .185	.285 .177	-.267 .208	-.350 .093	.603 .002	.922 <.001				
SN	-.372 .074	-.134 .532	.274 .195	.202 .344	.143 .506	.301 .152	-.319 .129	-.467 .021	.683 <.001					
Pons	-.214 .315	-.432 .035	-.135 .530	-.108 .616	-.129 .548	.537 .007	-.441 .031	-.477 .018						
Frontal	.177 .409	.062 .774	.068 .753	-.089 .678	-.237 .265	-.482 .037	.625 .001							
Parietal	.397 .055	.161 .451	.174 .416	.093 .665	-.001 .995	.522 .009								
Cerebell	.340 .104	.079 .714	.305 .147	-.249 .241	.223 .294									
BG	.240 .258	.343 .101	.757 <.001	.677 <.001										
Mes Temp	.392 .058	.390 .060	.856 <.001											
Lat Temp	-.366 .079	.388 .061												
Occiptal	.357 .087													

Table 3: Correlation of changes in cortical and subcortical regions during temporal lobe seizures. Pearson correlation coefficients (r), and significance levels (p, two-tailed t-test), respectively are listed as the top and bottom entries in each cell. Correlations were calculated between all possible pairs of anatomical regions ipsilateral to seizure onset across all 24 SPECT scans in the 21 patients. Regions with significant correlation at the 0.001 level are shown in white.

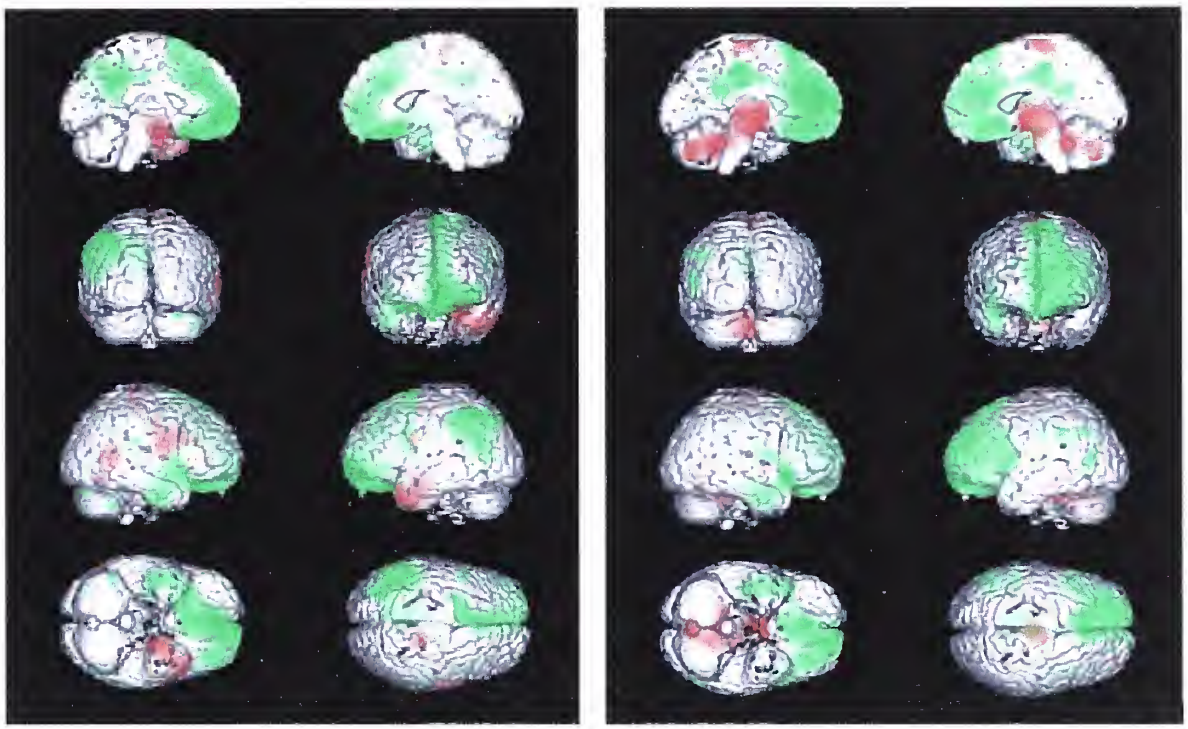

Figure 4: Complex partial seizures arising from the temporal lobe are associated with significant CBF increases and decreases in widespread brain regions. Statistical parametric maps depict CBF increases in red and decreases in green. Changes ipsilateral to seizure onset are shown on the left side of the brain, and contralateral changes on the right side of the brain (combining patients with left and right onset seizures). (**a**) 60-90s after seizure onset, increases occur mainly in the ipsilateral temporal lobe, while decreases occur in the ipsilateral > contralateral frontal and parietal association cortex (n=8). (**b**) >90s after seizure onset, increases occur mainly in the bilateral medial diencephalon, upper brainstem, and medial cerebellum, while decreases occur in the ipsilateral > contralateral frontal and parietal association cortex (n=10). For (a) and (b), extent threshold, k = 125 voxels (voxel size = 2x2x2 mm). Height threshold, p = 0.01. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed.

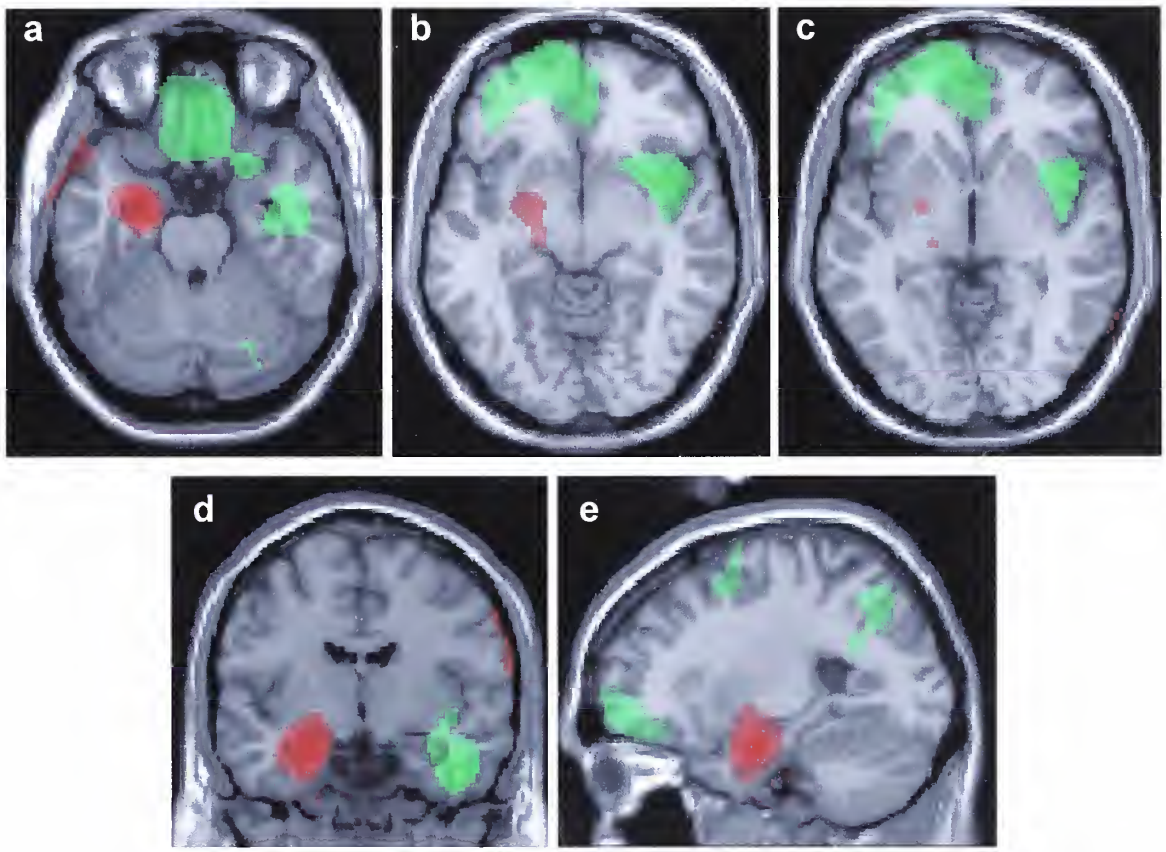

Figure 5: Cortical-subcortical involvement 60-90 seconds after onset of temporal lobe complex partial seizures. Same patient data as Fig. 4a (n=8). Statistical parametric maps depict CBF increases in red and decreases in green. Changes ipsilateral to seizure onset are shown on the left side of (**a-d**), and contralateral changes on the right side. (**a-c**) Horizontal sections progressing from inferior to superior showing CBF increases in the ipsilateral temporal lobe and ventral basal ganglia, and decreases in the bilateral association cortex. (**d**) Coronal section at the level of the pes hippocampi. (**e**) Sagittal section through the temporal lobe ipsilateral to seizure onset showing maximal involvement of the pes hippocampi. (**a-e**) Extent threshold, k = 125 voxels (voxel size = 2x2x2 mm). Height threshold, p = 0.01. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed.

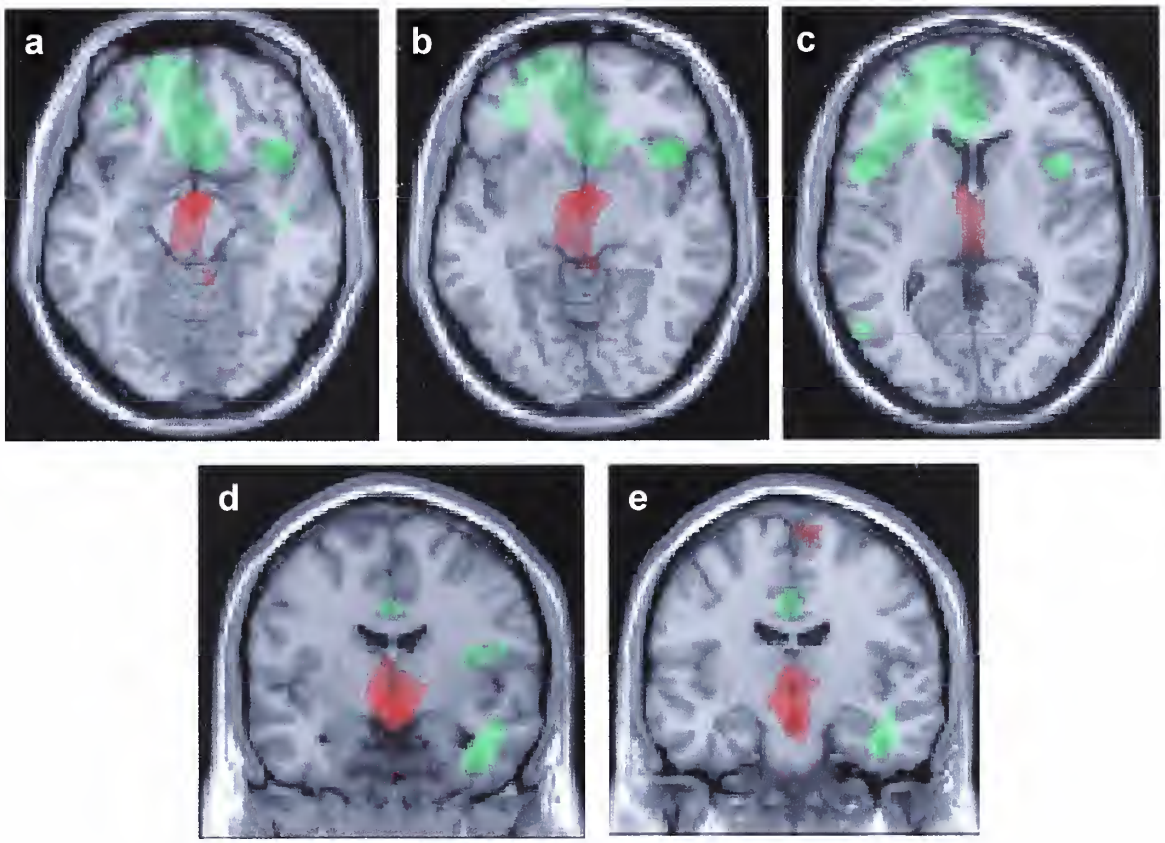

Figure 6: Cortical-subcortical involvement >90 seconds after onset of temporal lobe complex partial seizures. Same patient data as Fig. 4b (n=10). Statistical parametric maps depict CBF increases in red and decreases in green. Changes ipsilateral to seizure onset are shown on the left side, and contralateral changes on the right side of the figure. (**a-c**) Horizontal sections progressing from inferior to superior, and (**d-e**) coronal sections progressing from anterior to posterior showing CBF increases in the bilateral midbrain, hypothalamus, subthalamus (midbrain-diencephalic junction) and medial thalamus. Decreases are present in the bilateral association cortex. Extent threshold, k = 125 voxels (voxel size = 2x2x2 mm). Height threshold, p = 0.01. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed.

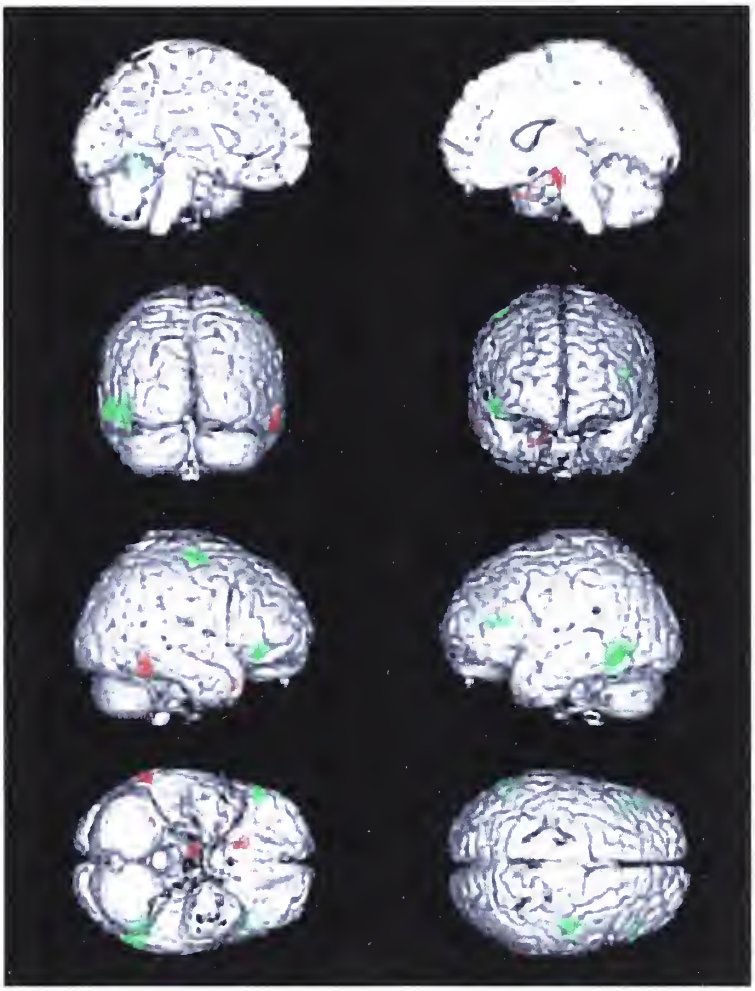

Figure 7: Simple partial seizures arising from the temporal lobe are not associated with widespread CBF changes. Statistical parametric maps depict CBF increases in red, and decreases in green (n=6). Changes ipsilateral to seizure onset are shown on the left side of the brain, and contralateral changes on the right side of the brain. Extent threshold, k = 125 voxels (voxel size = 2x2x2 mm). Height threshold, p = 0.01. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed. Resulting voxel clusters were not statistically significant after correction for multiple comparisons.

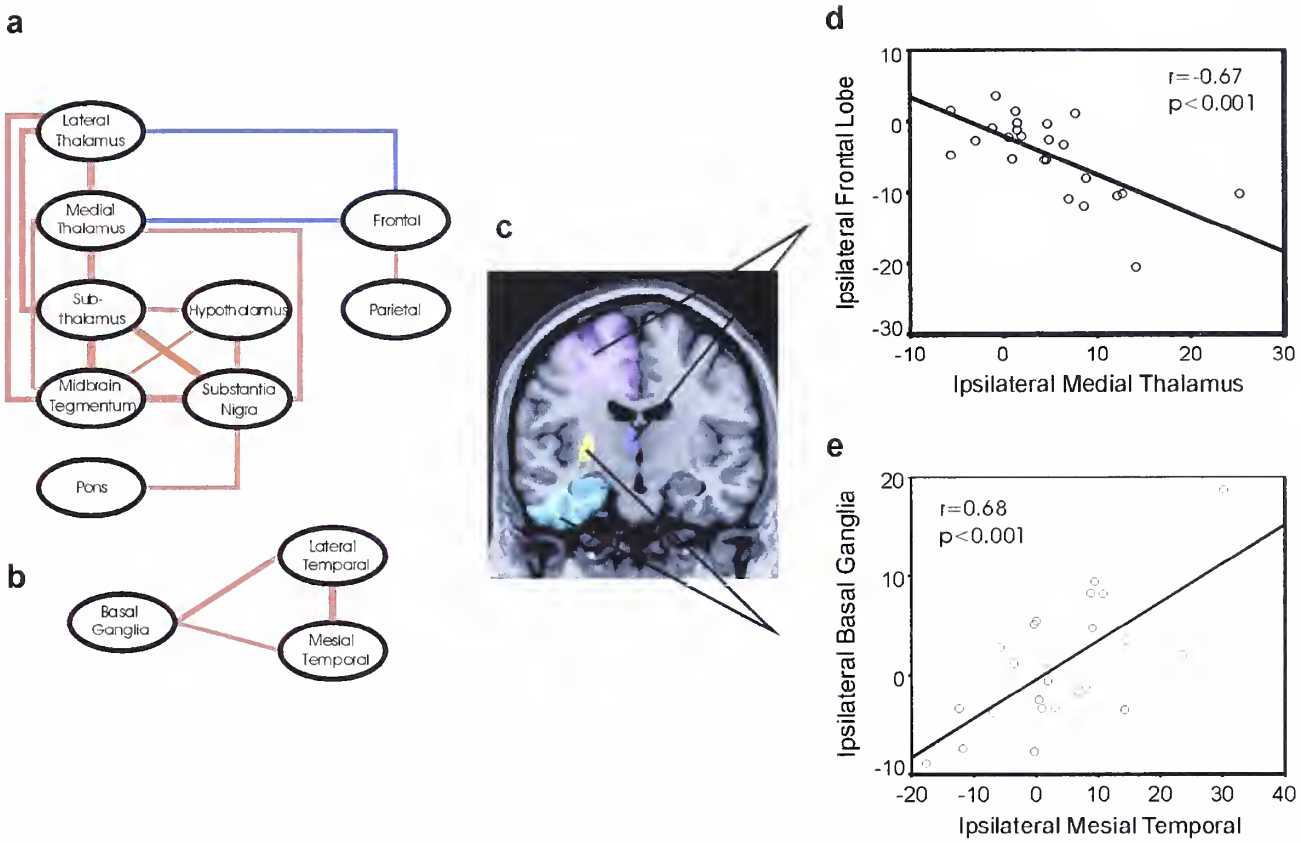

Figure 8: Cortical-subcortical network correlations in temporal lobe seizures. (**a**) Networks of midline subcortical structures, and fronto-parietal cortex ipsilateral to seizure onset showing positive (orange) and negative (blue) correlations (Table 1). Line thickness is proportional to the Pearson correlation coefficient (r). (**b**) Basal ganglia and temporal lobe also form a network of positive correlations. (**c-e**) Examples of correlations between pairs of structures ipsilateral to seizure onset. (**d**) Mean percent change (ictal vs. interictal) in the frontal lobe shows a significant negative correlation with mean percent change in the medial thalamus ($r = -0.67$, $p<0.001$; $n=24$). (**e**) Mean percent change in the basal ganglia shows a significant positive correlation with mean percent change in the mesial temporal lobe ($r = 0.68$, $p<0.001$; $n=24$).

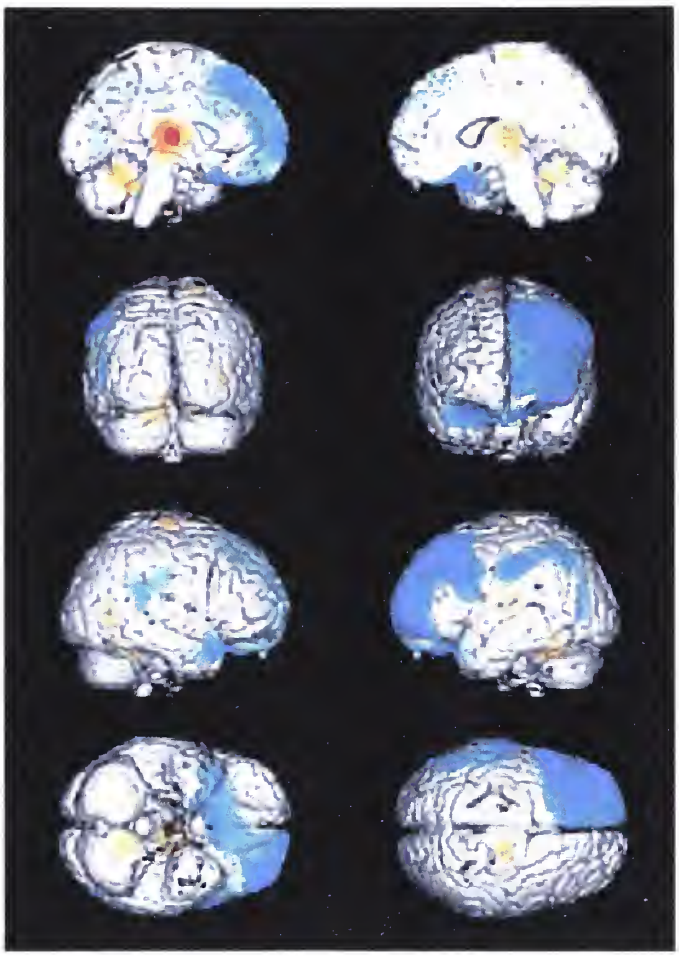

Figure 9: Brain regions showing significant correlation with ipsilateral medial thalamic perfusion changes in temporal lobe seizures. Statistical parametric map depicts positive correlations in orange and negative correlations in blue (n=24). The medial thalamus ipsilateral to seizure onset is shown in red. Significant positive correlations were seen at the cluster-level with the ipsilateral thalamus, subthalamus, midbrain, and medial cerebellum, as well as with the contralateral medial thalamus. Significant negative correlations were seen at the cluster-level with the bilateral orbital frontal, ipsilateral lateral frontal and parietal, and the contralateral temporal cortex. Extent threshold, k = 125 voxels (voxel size = 2x2x2 mm). Height threshold, p = 0.01. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed.

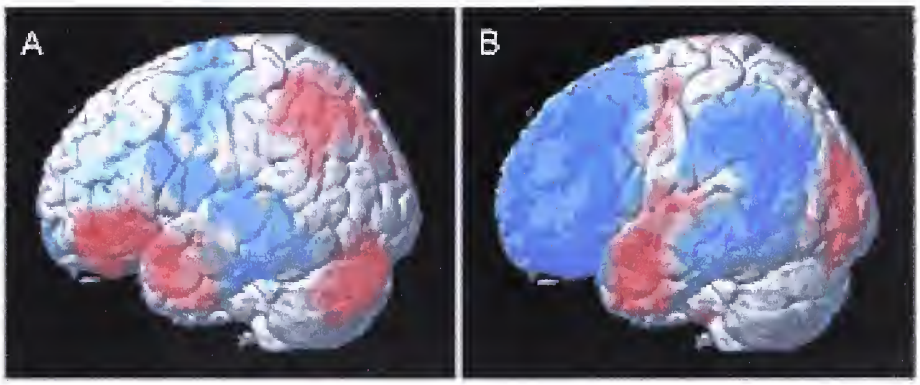

Figure 10: Fronto-parietal excitation in generalized tonic-clonic seizures and fronto-parietal inhibition in complex partial seizures. A, Tonic-clonic seizures causes abnormal cerebral blood flow increases (red) in the bilateral frontal and parietal association cortex. SPECT ictal-interictal difference imaging was obtained from a patient during a generalized tonic-clonic seizure induced by bilateral frontotemporal electroconvulsive therapy stimulation.[A] Bilateral cerebral blood flow increases (red) were present in the frontotemporal regions, the parietal cortex, and the cerebellum, with relative sparing, or cerebral blood flow decreases (blue) in intervening regions (left hemisphere only shown here). B, Complex-partial seizure causes abnormal cerebral blood flow decreases (blue) in bilateral frontal and parietal association cortex. SPECT ictal-interictal difference imaging was obtained from a patient during a complex partial seizure arising from the temporal lobe involved in this study. Cerebral blood flow increases were present in the temporal lobe of seizure onset, and marked decreases were present in the frontal and parietal cortex bilaterally (left hemisphere only shown here). Ictal and interictal SPECT images for A and B were acquired and analyzed using SPM. This figure is from, with permission of author, Blumenfeld, H. and J. Taylor, *Why do seizures cause loss of consciousness?* The Neuroscientist, 2003. 9(5).

[A] Blumenfeld, H., et al., *Targeted prefrontal cortical activation with bifrontal ECT.* Psychiat. Res. Neuroimag., 2003. 123(3): p 165-170.

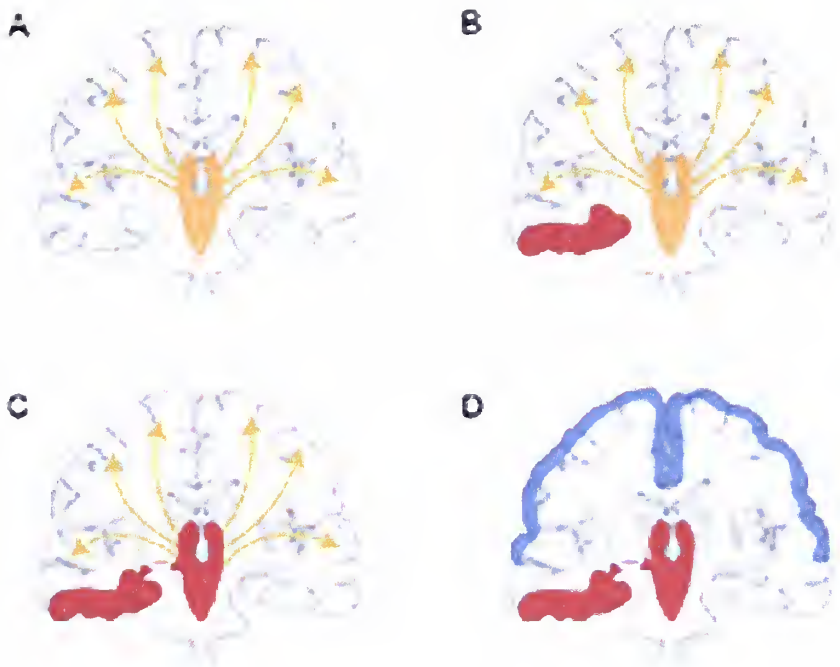

Figure 11: Network inhibition hypothesis for loss of consciousness in complex partial seizures. A, Under normal conditions, the upper brainstem-diencephalic activating systems interact with the cerebral cortex to maintain normal consciousness. B, A focal seizure involving the mesial temporal lobe unilaterally. C, Propagation of seizure activity from the mesial temporal lobe to midline subcortical structure. D, Disruption of the normal activating functions of the midline subcortical structures leads to depressed activity in bilateral regions of the fronto-parietal association cortex, leading to loss of consciousness. (Brain section modified with permission from Mai JK, Assheuer J, Paxinos G. 1997. *Atlas of the Human Brain.* San Diego, CA: Academic Press.) This figure is from, with permission of author, Blumenfeld, H. and J. Taylor, *Why do seizures cause loss of consciousness?* The Neuroscientist, 2003. 9(5).

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